



November 1, 2000

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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23, 12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The American College of Obstetricians and Gynecologists (ACOG) submits this petition to request that the Commissioner of the Food and Drug Administration take administrative action.

ACTION REQUESTED

This petition requests that the Commissioner of the Food and Drug Administration take administrative action to require the withdrawal of the letter which G.D. Searle issued on August 23, 2000 regarding its product, misoprostol. ACOG asks the FDA to review Searle's label of March 6, 2000 and particularly of June 29, 2000 and to rescind any contraindications for use of misoprostol in pregnancy that are not warranted by scientific evidence. Based on ACOG's review of the data, Searle's contraindications warrant analysis by FDA. ACOG requests that the re-labeling of misoprostol currently under review by the FDA conform with the agency's approval of the mifepristone-misoprostol combination on September 28, 2000, and ACOG's Statement of Grounds below.

STATEMENT OF GROUNDS

The American College of Obstetricians and Gynecologists is an organization representing more than 41,000 physicians dedicated to improving women's health care. ACOG is also the body which establishes standards of care for the ob-gyn profession. ACOG submits this recent review of actions by G.D. Searle regarding misoprostol and all adverse event data in the possession of the FDA:

"On August 23, 2000, G.D. Searle & Co. issued a letter entitled "Important Drug Warning Concerning Unapproved Use of Intravaginal or Oral Misoprostol in Pregnant Women for Induction of Labor or Abortion." This letter cautions that Cytotec (misoprostol) is indicated for prevention of non-steroidal-antiinflammatory-drug-induced gastric ulcers and states, "...Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion." The letter further states that Searle has become aware of the drug's use for induction of labor or as a cervical ripening agent prior to termination of pregnancy. Moreover, the letter notes serious adverse events, including uterine hyperstimulation and uterine rupture, which have resulted in fetal and maternal death. Finally, the company cautions, "In addition to the

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known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth, development, and functional maturation of the child when Cytotec is used for induction of labor or cervical ripening has not been established.”

The American College of Obstetricians and Gynecologists (ACOG) is concerned by the content, timing, and tone of this letter. Given that misoprostol is commonly employed in conjunction with mifepristone (RU 486) to achieve nonsurgical early pregnancy terminations, the arrival of the Searle letter within weeks of the U.S. Food and Drug Administration's (FDA) approval of mifepristone could limit the use of this new option for reproductive choice. Also, although the letter correctly points out the potentially serious, but relatively rare, risks of misoprostol when employed for cervical ripening and labor induction, it fails to comment on the extensive clinical experience with this agent and the large body of published reports supporting its safety and efficacy when used appropriately. A recent review of the Cochrane Pregnancy and Childbirth group trials registry identified 26 clinical trials of misoprostol for cervical ripening or induction of labor or both (1). These studies indicate misoprostol is more effective than prostaglandin E₂ in achieving vaginal deliveries within 24 hours and reduces the need for and total amount of oxytocin augmentation. Although these studies do suggest misoprostol is associated with a higher incidence of uterine hyperstimulation and meconium-stained amniotic fluid, these complications were more common with higher doses (>25 µg) of misoprostol. Other recent reviews and clinical trials support these conclusions (2-4). No studies indicate that intrapartum exposure to misoprostol (or other prostaglandin cervical ripening agents) has any long-term adverse health consequences to the fetus in the absence of fetal distress, nor is there a plausible biological basis for such a concern.

A review of published reports and of MedWatch, the FDA medical products reporting program, indicates the vast majority of adverse maternal and fetal outcomes associated with misoprostol therapy resulted from the use of doses greater than 25 µg, dosing intervals more frequent than 3–6 hours, addition of oxytocin less than 4 hours after the last misoprostol dose, or use of the drug in women with prior cesarean delivery or major uterine surgery. Grand multiparity also appears to be a relative risk factor for uterine rupture.

Thus, based on recently published series and a detailed review of adverse outcomes reported to the FDA, the ACOG Committee on Obstetric Practice strongly endorses its previous conclusions, published in Committee Opinion Number 228 (November 1999), *Induction of Labor with Misoprostol*, which states, “*Given the current evidence, intravaginal misoprostol tablets appear effective in inducing labor in pregnant women who have unfavorable cervixes*” (5). Nonetheless, the Committee would like to emphasize that the following clinical practices appear to minimize the risk of uterine hyperstimulation and rupture in patients undergoing cervical ripening or induction in the third trimester:

- 1) If misoprostol is to be used for cervical ripening or labor induction in the third trimester, one quarter of a 100µg tablet (ie, approximately 25µg) should be considered for the initial dose.
- 2) Doses should not be administered more frequently than every 3-6 hours.
- 3) Oxytocin should not be administered less than 4 hours after the last misoprostol dose.
- 4) Misoprostol should not be used in patients with a previous cesarean delivery or prior major uterine surgery.

The use of higher doses of misoprostol (eg, 50 µg every 6 hours) to induce labor may be appropriate in some situations, although there are reports that such doses increase the risk of complications, including uterine hyperstimulation and uterine rupture (6). There is insufficient clinical evidence to address the safety or efficacy of misoprostol in patients with multifetal gestations or suspected fetal macrosomia.

In conclusion, the ACOG Committee on Obstetric Practice reaffirms that misoprostol is a safe and effective agent for cervical ripening and labor induction when used appropriately. Moreover, misoprostol also contributes to the obstetrician-gynecologist's resources as an effective treatment for serious postpartum hemorrhage in the presence of uterine atony (7-12)."

ENVIRONMENTAL IMPACT

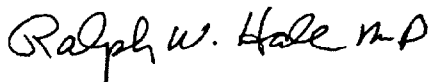
The proposed action is exempt from the requirement of an environmental impact statement under 21 CFR §§ 25.24 (a)(8) and (c)(6).

ECONOMIC IMPACT

No information is required at this time.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Ralph W. Hale, MD, FACOG
American College of Obstetricians and Gynecologists
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Attachments: References
G.D. Searle letter 8/23/00
Rep. Coburn letter 10/16/00

References

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SEARLE

**IMPORTANT DRUG WARNING
CONCERNING UNAPPROVED USE OF INTRAVAGINAL
OR ORAL MISOPROSTOL IN PREGNANT WOMEN
FOR INDUCTION OF LABOR OR ABORTION**

SEARLE
5200 OLD ORCHARD ROAD
SAUNEL, ILLINOIS 60077
PHONE (847) 982-7000
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August 23, 2000

Re: Cytotec® (misoprostol)

Dear Health Care Practitioner:

The purpose of this letter is to remind you that Cytotec administration by any route is contraindicated in women who are pregnant because it can cause abortion. Cytotec is not approved for the induction of labor or abortion.

Cytotec is indicated for the prevention of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.

The uterotonic effect of Cytotec is an inherent property of prostaglandin E₁ (PGE₁), of which Cytotec is a stable, orally active, synthetic analog. Searle has become aware of some instances where Cytotec, outside of its approved indication, was used as a cervical ripening agent prior to termination of pregnancy, or for induction of labor, in spite of the specific contraindications to its use during pregnancy.

Serious adverse events reported following off-label use of Cytotec in pregnant women include maternal or fetal death; uterine hyperstimulation, rupture or perforation requiring uterine surgical repair, hysterectomy or salpingo-oophorectomy; amniotic fluid embolism; severe vaginal bleeding, retained placenta, shock, fetal bradycardia and pelvic pain.

Searle has not conducted research concerning the use of Cytotec for cervical ripening prior to termination of pregnancy or for induction of labor, nor does Searle intend to study or support these uses. Therefore, Searle is unable to provide complete risk information for Cytotec when it is used for such purposes. In addition to the known and unknown acute risks to the mother and fetus, the effect of Cytotec on the later growth, development and functional maturation of the child when Cytotec is used for induction of labor or cervical ripening has not been established.

Searle promotes the use of Cytotec only for its approved indication. Please read the enclosed updated complete Prescribing Information for Cytotec.

Further information may be obtained by calling 1-800-323-4204.



Michael Cullen, MD
Medical Director, U.S.
Searle

CY20141A

TOM A. COBURN, M.D.
2D DISTRICT, OKLAHOMA

COMMITTEE ON COMMERCE
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October 16, 2000

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Ralph W. Hale, MD, FACOG
Executive Vice President
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Dear Dr. Hale,

Thank you for your letter stating ACOG's opposition to H.R. 5385 and S. 3157, the RU-486 Patient Health and Safety Act. Of course, I am not surprised by ACOG's opposition to this legislation because I am familiar with July 27, 2000 communication from ACOG to the FDA regarding the patient protection guidelines the FDA was reportedly considering. As you can see, my bill is nothing other than an attempt to codify most of those very same guidelines.

Each one of those guidelines has but one purpose: the protection of patient health and safety. It was a sad day when the FDA approved RU-486 — the first drug ever approved for the specific purpose of ending a human life. But that was made even worse by the fact that the FDA succumbed to the political pressure brought by ACOG and other elements of the abortion lobby by dropping most of the proposed patient protections, and thereby recklessly exposing women to avoidable risk.

Let us review the patient protection standards to which you objected and which the FDA dropped under that pressure, evidently in response to those objections.

1) Limit distribution of the drug only to licenced physicians. The point of this, obviously, is to ensure that mifepristone is administered only under a doctor's direct supervision. The FDA actually retained this standard, but your objection to it raises very troubling concerns about ACOG's commitment to patient protection.

2) Require the physician to be "trained and authorized by law" to provide surgical abortions. I am surprised that ACOG would object either to training or legal authorization for a physician. The legal authorization is a matter of state law. As for training in abortion procedures, the real issue in connection with a mifepristone/misoprostol abortion is the ability to handle complications, and especially the ability to perform a dilatation and curettage in the event of an incomplete abortion — a rather common complication, according to the clinical trials. I have dealt with this in my bill by adding to the original FDA proposal a distinct requirement that the prescribing physician be qualified to handle the complications of an incomplete abortion or an ectopic pregnancy.

My bill does not address the paradox that the FDA has approved a drug which, used by itself, is not efficacious in achieving the intended purpose of a completed abortion, and which becomes effective only when used in combination with another drug whose manufacturer has warned is unsafe in that application. The FDA cannot escape the logical dilemma of having approved a drug that is either ineffective (when used without misoprostol) or unsafe (when used with misoprostol).

Your justification for authorizing the use of misoprostol for chemically inducing abortion is that without misoprostol, mifepristone is ineffective. That is what is known as circular reasoning.

The evidence that we have from the clinical trials about the safety of the mifepristone/misoprostol combination for abortion is not entirely encouraging. There were no deaths among the sample population, but the rate of incomplete abortions was nearly 8 percent and the incidence of hemorrhaging was 5 percent. These are both potentially serious complications with rates of occurrence that are too high to be dismissed as "rare." In France, where far more stringent safety precautions are in effect, one death and two near-fatal cardiac arrests were recorded within the first two years of availability. In 1991, in response to concerns about such complications, France banned the use of mifepristone by women over 35 and by smokers. The U.S. clinical trials reportedly did not include smokers or women over 35 among the subjects, but neither of these conditions is listed in the label, the prescriber's agreement, the patient agreement, or the medication guide as a contraindication. Undoubtedly, some women from both of those risk categories will be likely to receive the drug combination because neither they nor their doctors have any way of knowing these factors pose an additional risk.

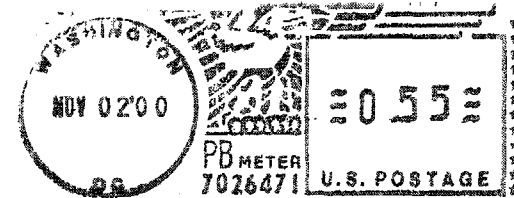
You will note that my legislation does not at all address the question of the use of misoprostol to induce labor. As a practitioner, I am grateful to Searle for calling attention to the risks and contraindications of induction with misoprostol. But I am also cognizant of the benefits of using misoprostol for induction in some cases. The freedom of doctors to weigh the risks and benefits and then to act in the best interest of their patients is not at all affected by my legislation and is irrelevant to the conditions under which mifepristone was approved.

I have no doubt that if women were asked whether their doctor should have to be able to read a sonogram, handle complications, and get them admitted to a hospital in case of emergency, they would not hesitate to demand those levels of competence. Nor do I have any doubt that women would expect their doctors to be trained in the use of a potentially risky drug. In light of the very real and very serious risks to maternal health associated with this method of abortion, I remain amazed and dismayed that ACOG opposes the elementary patient protection standards that I have proposed. I encourage you to reconsider your position.

Sincerely,

Tom A. Coburn, M.D.
Member of Congress

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